COMPOSITION & USE FOR REDUCING ADENOSINE LEVELS & TREATING ASTHMA & OTHER DISEASES & CONDITIONS AFFLICTING THE AIRWAYS WITH AN EPIANDROSTERONE, A UBIQUINONE, OR BOTH

Field of the Invention

This invention concerns itself with a method of treating adenosine depletion by administration of folinic acid or a pharmaceutically acceptable salt thereof. This invention further concerns itself with a method of treating asthma by administering dehydroepiandrosterone, analogs thereof, or their pharmaceutically acceptable salts and/or ubiquinone.

Description of the Invention

Adenosine is a purine which contributes to intermediary metabolism and participates in the regulation of physiological activity in a variety of mammalian tissues. Adenosine participates in many local regulatory mechanisms, such as those occuring in synapses in the central nervous system (CNS) and at neuroeffector junctions in the peripheral nervous system. In the CNS, adenosine inhibits the release of a variety of neurotransmitters, such as acetylcholine, noradrenaline, dopamine, serotonin, glutamate, and GABA; depresses neurotransmission; reduces neuronal firing to induce spinal analgesia and possesses anxiolytic properties. *See* A. Pelleg and R. Porter, *Pharmacotherapy* 10(2), 157 (1990); J. Daval, *et al.*, *Life Sciences* 49:1435 (1991). In the heart, adenosine suppresses pacemaker activity, slows AV conduction, possesses antiarrhythmic and arrhythmogenic effects, modulates autonomic control and triggers the synthesis and release of prostaglandins. *See* K. Mullane and M. William, *Adenosine and Adenosine Receptors p.* 289 (M. Williams, ed. Humana Press, 1990). In addition, adenosine has potent vasodilatory effects and modulates vascular tone. *See* A Deuseen et al., *J. Pflugers Arch.* 406: 608 (1986). Adenosine is currently being used clinically for the treatment of supraventricular tachycardia and other cardiac anomalies. *See* C. Chronister, *American Journal of Critical Care 2(1):* 41-47

(1993). Adenosine analogues are also being investigated for use as anticonvulsant, anxiolytic and neuroprotective agents. See, M. Higgins et al., *Pharmacy World & Science* 16 (2): 62-68 (1994).

Adenosine has also been implicated as a primary determinant underlying the symptoms of bronchial asthma. It induces bronchoconstriction and the contraction of airway smooth muscle. See J. Thorne and K. Broadley, *American Journal of Respiratory & Critical Care Medicine* 149(2 pt. 1): 392-399 (1994); S. Ali et al., *Agents & Actions* 37 (304): 165-167 (1992). Adenosine causes bronchoconstriction in asthmatics but not in non-asthmatics. See *Bjorck* et al., *American Review of Respiratory Disease* 145 (5): 1087-1091 (1992); S. Holgate et al., *Annals of the New York Academy of Sciences* 629: 227-236 (1991).

In view of the foregoing, it is readily apparent that *(i)* adenosine depletion may lead to a broad variety of deleterious conditions, and that methods of treating adenosine depletion may be an extremely useful means of therapeutic intervention; and *(ii)* methods of inducing adenosine depletion may also be useful in treating conditions such as asthma. Folinic acid is an intermediate product of the metabolism of folic acid; the active form into which that acid is converted in the body. Ascorbic acid is required as a necessary factor in the conversion process. Folinic acid has been used therapeutically as an antidote to folic acid antagonists such as methotrexate which block the conversion of folic acid into folinic acid. Additionally, folinic acid has been used as an anti-anemic (combating folate deficiency). Se The Merck Index, Monograph No. 4141 (11th Ed. 1989). The use of folinic in patients afflicted with adenosine depletion, or in a method to therapeutically elevate adenosine levels in the brain or

other organ, has heretofor neither been suggested nor described.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating adenosine depletion in a subject in need of such treatment that comprises administering to the subject folinic acid or a pharmaceutically acceptable salt thereof in an amount effective to treat the adenosine depletion. The method may be applied to subjects afflicted with steroid-induced adenosine depletion, subjects afflicted with anxiety, subjects afflicted with a wasting disorder, or subjects afflicted with any other disorder attributable to adenosine depletion, or where an increase in adenosine levels would be therapeutically beneficial.

The present invention also relates to the use of folinic acid or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating adenosine depletion in a subject in need of such treatment as set forth above.

The present invention, moreover, relates to a method of treating asthma in a subject in need of such treatment by administering to the subject dehydroepiandrosterone, an analog thereof, or a pharmaceutically acceptable salt thereof, in an amount effective to treat asthma.

The present invention also relates to the use of dehydroepiandrosterone, an analog thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating asthma.

The present invention also relates to the use of a ubiquinone (CoQn, where n=1-12) in the preparation of a medicament, and to the use of the medicament for the treatment of adenosine depletion and of airway disease.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The method of treating adenosine depletion disclosed herein may be used to treat steroid-induced adenosine depletion, to stimulate adenosine synthesis and thereby treat or control anxiety (e.g., in treating premenstrual syndrome); to increase weight gain or treat

wasting disorders; and to treat other adenosine-related pathologies by administering folinic acid. Thus, the term "adenosine depletion" is intended to encompass both conditions where adenosine levels are depleted in the subject as compared to previous adenosine levels in that subject, and conditions where adenosine levels are essentially the same as previous adenosine levels in that subject but, because of some other condition or alteration in that patient, a therapeutic benefit would be achieved in the patient by increased adenosine levels as compared to previous levels. Preferably, the method is carried out on patients where adenosine levels are depleted as compared to previous adenosine levels in that subject. The present invention is concerned primarily with the treatment of human subjects but may also be employed for the treatment of other mammalian subjects, such as dogs and cats, for veterinary purposes.

Folinic acid and the pharmaceutically acceptable salts thereof (hereafter sometimes referred to as "active compounds") are known, and can be made in accordance with known procedures. *See generally* THE Merck Index, Monograph No. 4141 (11th Ed. 1989); U.S. Patent No. 2,741,608.

Pharmaceutically acceptable salts should be both pharmacologically and pharmaceutically acceptable. Such pharmacologically and pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline each salts, such as sodium, potassium, or calcium salts, of the carboxylic acid group of Folinic acid. The calcium salt of folinic acid is a preferred pharmaceutically acceptable salt.

The active compounds are preferably administered to the subject as a pharmaceutical composition. Pharmaceutical compositions for use in the present invention include those suitable for inhalation, oral, topical (including buccal, sublingual, dermal and intraocular) parenteral (including subcutaneous,

intradermal, intramuscular, intravenous and intraarticular) and transdermal administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art.

Compositions suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such compositions may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier. In general, the compositions of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid binder. Compositions for oral administration may optionally include enteric coatings known in the art to prevent degradation of the compositions in the stomach and provide release of the drug in the small intestine.

Compositions suitable for buccal (sub-lingual) administration include lozenges comprising the active compound in a flavored base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in

an inert base such as gelatin and glycerin or sucrose and acacia.

Compositions suitable for parenteral administration comprise sterile aqueous and non-aqueous injection solutions of the active compound, which preparations are preferably isotonic with the blood of the intended recipient. These preparations may contain anti-oxidants, buffers, bacteriostats and solutes which render the compositions isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or water-for-injection immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

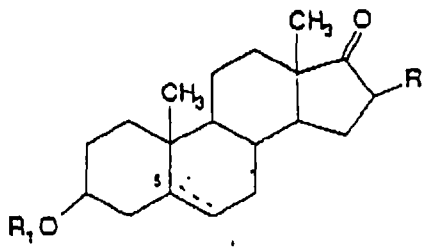
Compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanoline, polyethylene glycols, alcohols, transdermal enhancers, and combinations of two or more thereof.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Compositions suitable for transdermal administration may also be delivered by iontophoresis (see, e.g., *Pharmaceutical Research* 3, 318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound.

Dosage will vary depending on age, weight, and condition of the subject. Treatment may be initiated

with small dosages less than optimum dose and increased until the optimum effect under the circumstances is reached. In general, the dosage will be from 1, 5, 10, or 20 mg/kg subject body weight, up to 100, 200, 500 or 1000 mg/kg subject body weight. Currently, dosages of from 5 to 500 mg/kg are preferred, dosages of from 10 to 200 mg/kg are more preferred, and dosages of from 20 to 100 mg/kg are most preferred. In general, the active compounds are preferably administered at a concentration that will afford effective results without causing any unduly harmful or deleterious side effects, and may be administered either as a single unit dose, or if desired, in convenient subunits administered at suitable times throughout the day.

Also disclosed herein is a method of reducing adenosine levels, particularly in the lung, liver, heart and brain and, therefore of treating asthma, particularly non-steroid dependent asthma, by administering to a subject in need of such treatment dehydroepiandrosterone (DHEA), an analog thereof, or a pharmaceutically acceptable salt thereof, in an amount effective to inhibit or control asthma to that subject. Examples of DHEA and analogs thereof that may be used to carry out this method are represented by the formula:



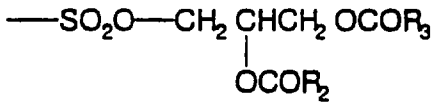
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wherein:

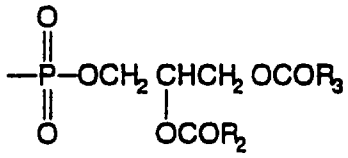
the broken line represents an optional double bond;

R is hydrogen or a halogen;

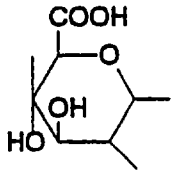
R_1 is hydrogen or an SO_2OM group where M is hydrogen, M is sodium, M is a sulphatide group:



M is a phosphatide group:



wherein each of R_2 and R_3, which may be the same or different, is a straight or branched chain alkyl radical of 1 to 14 carbon atoms, or a glucuronide group:



The hydrogen atom at position 5 of Formula I is present in the alpha or beta configuration or the compound comprises a mixture of both configurations. Compounds illustrative of Formula (I) above include:

DHEA, wherein R and R_1 are each hydrogen and the double bond is present;

16-alpha bromoepiandrosterone, wherein R is Br, R_1 is H, and the double bond is present;

16-alpha-fluoroepiandrosterone, wherein R is F, R_1 is H and the double bond is present;

etiocholanolone, wherein R and R_1 are each hydrogen and the double bond is absent;

dehydroepiandrosterone sulphate, wherein R is H, R_1 is SO_2OM and M is a sulphatide group as defined above, and the double bond absent. Preferably, in the compound of Formula I, R is halogen (*e.g.*, bromo, chloro, or fluoro), R_1 is Hydrogen, and the double bond is present. Most preferably the compound of Formula I is 16-alpha-fluoroepiandrosterone.

The compounds of Formula I are made in accordance with known procedures or variations thereof that will be apparent to those skilled in the art. *See* U.S. Patent No. 4,956,355, UK Patent No. 2,240,472, EPO Patent Appln No. 429,187, PCT Patent Appln No. 91/04030; *see also* M. Abou-Gharbia et al., *J. Pharm. Sci.* 70, 1154-1157 (1981), Merck Index Monograph No. 7710 (11th ed. 1989).

The compounds used to treat asthma may be administered per se or in the form of pharmaceutically acceptable salts, as discussed above (the two together again being referred to as "active compounds"). The active compounds salts may be administered either systemically, as discussed above, or to the lungs of the subject as discussed below. In general, the active compounds salts are administered in a dosage of 1 to 3600 mg/kg body weight, more preferably about 5 to 1800 mg/kg, and most preferably about 20 to 100 mg/kg. The active compounds may be administered once or several times a day.

The active compounds disclosed herein may be administered to the lungs of a subject by any suitable means, but are preferably administered by generating an aerosol comprised of respirable particles, the respirable particles comprised of the active compound, which particles the subject inhales (*i.e.*, by inhalation administration). The respirable particles may be liquid or solid.

Particles comprised of active compound for practicing the present invention should include particles

of respirable size: that is, particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. In general, particles ranging from about .5 to 10 microns in size (more particularly, less than about 5 microns in size) are respirable. Particles of non-respirable size which are included in the aerosol tend to deposit in the throat and be swallowed, and the quantity of non-respirable particles in the aerosol is preferably minimized. For nasal administration, a particle size in the range of 10-500 μm is preferred to ensure retention in the nasal cavity.

Liquid pharmaceutical compositions of active compound for producing an aerosol may be prepared by combining the active compound with a suitable vehicle, such as sterile pyrogen free water. Solid particulate compositions containing respirable dry particles of micronized active compound may be prepared by grinding dry active compound with a mortar and pestle, and then passing the micronized composition through a 400 mesh screen to break up or separate out large agglomerates. A solid particulate composition comprised of the active compound may optionally contain a dispersant which serves to facilitate the formation of an aerosol. A suitable dispersant is lactose, which may be blended with the active compound in any suitable ratio (e.g., a 1 to 1 ratio by weight).

Aerosols of liquid particles comprising the active compound may be produced by any suitable means, such as with a nebulizer. *See, e.g.*, U.S. Patent No. 4,501,729. Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable compositions for use in nebulizers consist of the active ingredient in

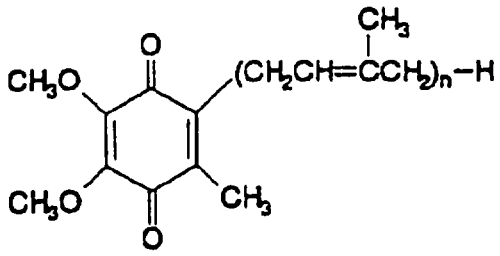
a liquid carrier, the active ingredient comprising up to 40% w/w of the compositions, but preferably less than 20% w/w/. The carrier is typically water or a dilute aqueous alcoholic solution, preferable made isotonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the compositions is not prepared sterile, for example, methyl hydroxybenzoate, antioxidants, flavoring agents, volatile oils, buffering agents and surfactants.

Aerosols of solid particles comprising the active compound may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particluate medicaments to a subject produce particles which are respirable, as explains above, and generate a volume of aerosol containing a predetermined metered dose of medicament at a rater suitable for human administration. Examples of such aerosol generators include metered dose inhalers and insufflators.

Ubiquinone may be administered concurrently with the DHEA or analog thereof in the methods of treating asthma described above. The phrase "concurrently administering," as used herein means that the DHEA or the DHEA analog are administered either (a) simultaneously in time (preferably by formulating the two together in a common pharmaceutical carrier), or (b) at different times during the course of a common treatment schedule. In the latter case, the two compounds are administered at times sufficiently close for the ubiquinone to offset ubiquinone depletion in the lungs (and heart) of the subject and thereby counterbalance any deterioration of lung (and heart) function that may result from the administration of the DHEA or the analog thereof. The term "ubiquinone", as used herein, refers to a family of compounds having structures based on a 2,3-0dimethoxy-5-methylbenzoquinone nucleus with a variable terpenoid acid chain containing on to twelve

21 MAR 2003

mono-unsaturated trans-isoprenoid units. Such compounds are known in the art as "Coenzyme Qn", in which n equals 1 to 12. These compounds may be referred to herein as compounds represented by the formula:



wherein n = 1 to 10. Preferably, in the method of the invention, the ubiquinone is a compound according to formula given above, wherein n = 6 to 10 (e.g., Coenzymes Q6-10), and most preferably wherein n = 10 (i.e., Coenzyme Q10).

Where the ubiquinone is formulated with a pharmaceutically acceptable carrier separately from the DHEA, analog thereof, or salt thereof (e.g., where the DHEA analog thereof or salt thereof is administered to the lungs of the subject, and the ubiquinone is administered systemically) it may be formulated by any of the techniques set forth above.

In general, the ubiquinone is administered in an amount effective to offset ubiquinone depletion in the lungs and heart of the subject induced by the DHEA, analog thereof, or salt thereof, and the dosage will vary depending upon the condition of the subject and the route of administration. The ubiquinone is preferably administered in a total amount per day of about 1 to 1200 mg/kg body weight, more preferably about 30 to 600 mg/kg, and most preferably about 50 to 150 mg/kg. The ubiquinone may be administered once or several times a day.

The following examples are provided to more fully illustrate the present invention and should not be construed as restrictive thereof. In the following examples, DHEA means dehydroepiandrosterone, s means seconds, mg means milligrams, kg means kilograms, kW means kilowatts, MHz means megahertz, and nmol means nanomoles.

EXAMPLES 1 AND 2

Effects of Folinic Acid and DHEA on Adenosine Levels *In vivo*

Young adult male Fischer 344 rats (120 grams) were administered dehydroepiandrosterone (DHEA) (300 mg/kg) or methyltestosterone (40 mg/kg) in carboxymethylcellulose by gavage once daily for fourteen days. Folinic acid (50 mg/kg) was administered intraperitoneally once daily for fourteen days. On the fifteenth day, the animals were sacrificed by microwave pulse (1.33 kW, 2450 MHz, 6.5 s) to the cranium, which instantly denatures all brain protein and prevents further metabolism of adenosine. Hearts were removed from animals and flash frozen in liquid nitrogen within 10 seconds of death. Liver and lungs were removed *en bloc* and flash frozen within 30 seconds of death. Brain tissue was subsequently dissected. Tissue adenosine was extracted, derivatized to 1,N^6-ethenoadenosine and analyzed by high performance liquid chromatography (HPLC) using spectrofluorometric detection according to the method of Clark and Dar (*J. of Neuroscience Methods* 25:243 (1988)). Results of these experiments are summarized in **Table 1** below. Results are expressed as the mean ± SEM, with χ $p<0.05$ compared to control group and ϕ $p<0.05$ compared to DHEA or methyltestosterone-treated groups.

TABLE 1. Effects of DHEA, δ-1-methyltestosterone and folinic acid on adenosine levels in various tissues of the rat.

Treatment	Intracellular adenosine (nmols)/mg protein			
	Heart	Liver	Lung	Brain
Control	10.6 ±0.6 (n=12)	14.5 ±1.0 (n=12)	3.1 ±0.2 (n=6)	0.5 ±0.04 (n=12)
DHEA (300 mg/kg)	6.7 ±0.5 (n=12)ψ	16.4 ±1.4 (n=12)	2.3 ±0.3 (n=6)ψ	0.19 ±0.01 (n=12)ψ
Methyltestosterone (40 mg/kg)	8.3 ±1.0 (n=6)ψ	16.5 ±0.9 (n=6)	N.D.	0.42 ±0.06 (n=6)
Methyltestosterone (120 mg/kg)	6.0 ±0.4 (n=6)ψ	5.1 ±0.5 (n=6)ψ	N.D.	0.32 ±0.03 (n=6)ψ
Folinic Acid (50 mg/kg)	12.4 ±2.1 (n=5)	16.4 ±2.4 (n=5)	N.D.	0.72 ±0.09 (n=5)ψ
DHEA (300 mg/kg) + Folinic Acid (50 mg/kg)	11.1 ±0.6 (n=5)φ	18.8 ±1.5 (n=5)φ	N.D.	0.55 ±0.09 (n=5)φ
Methyltestosterone (120 mg/kg) + Folinic Acid (50 mg/kg)	9.1 ±0.4 (n=6)φ	N.D.	N.D.	0.60 ±0.06 (n=6)φ

The results of these experiments indicate that rats administered DHEA or methyltestosterone daily for two weeks showed multi-organ depletion of adenosine. Depletion was dramatic in brain (60% depletion for DHEA, 34% for high dose methyltestosterone) and heart (37% depletion for DHEA, 22% depletion for high dose methyltestosterone). Co-administration of folinic acid completely abrogated steroid-mediated adenosine depletion. Folinic acid administered alone induce increases in adenosine levels for all organs studied.

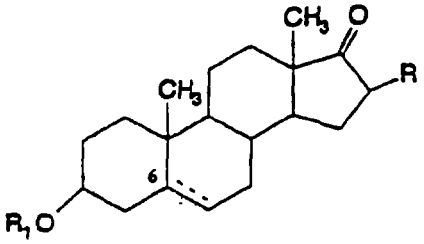
The foregoing examples are illustrative of the present invention, and are not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

21 MAR 2003

CLAIMS

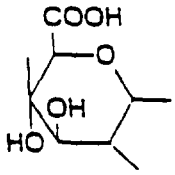
1. An inhalable, respirable, intrapulmonary, nasal, topical or transdermal pharmaceutical composition, used for regulating levels of adenosine or adenosine receptor, reducing hypersensitivity to adenosine, preventing or treating a disease or condition of the heart, liver, lung(s) or brain, comprising a pharmaceutically or veterinarily acceptable carrier, and an active agent selected from the group consisting of

an epiandrosterone of the chemical formula



(I)

wherein the broken line represents a single or a double bond; R is hydrogen or a halogen; the H at position 5 is present in the alpha or beta configuration or the compound of chemical formula I comprises a racemic mixture of both configurations; and R^1 is hydrogen or SO_2OM, wherein M is selected from the group consisting of H, Na, sulphatide of the formula $-SO_2O-CH_2CHCH_2OCOR^3$ (with $OCOR^2$) and phosphatide of the formula $-P(=O)(OH)-OCH_2CHCH_2OCOR^3$ (with $OCOR^2$), wherein R^2 and R^3, which may be the same or different, are straight or branched (C_1-C_{14}) alkyl or glucuronide of the formula



;

a ubiquinone (CoQn), wherein n=1-12; or

folinic acid or a pharmacueitcally or veterinarily acceptable salt thereof.

2. The composition of claim 1, further comprising an active agent selected from the group consisting of antioxidants, flavoring agents, volatile oils, buffering agents, dispersants, surfactants, propellants and preservatives.

3. The composition of claim 1, wherein the active agent comprises a compound of formula I is selected from the group consisting of dehydroepiandrosterone, 16-alpha-bromoepiandrosterone, 16-alpha-fluoro epiandrosterone, etiocholanolone, dehydroepiandrosterone sulphate and pharmaceutically acceptable salts thereof.

4. The composition of claim 1, wherein the active agent comprises a compound of formula (I) is dimethyl epiandosterone (DHEA), wherein R and R^1 are each hydrogen and the broken line represents a double bond, or a pharmaceutically or veterinarily acceptable salt thereof.

5. The composition of claim 1, wherein the active agent comprises a compound of formula I is 16-alpha bromoepiandrosterone, wherein R is Br, R^1 is H, and the broken line represents a double bond, or a pharmaceutically or veterinarily acceptable salt thereof.

6. The composition of claim 1, wherein the active agent comprises a compound of formula I is 16-alpha-fluoro epiandrosterone, wherein R is F, R^1 is H and the broken line represents a double bond, or a pharmaceutically or veterinarily acceptable salt thereof.

7. The composition of claim 1, wherein the active agent comprises a compound of formula I is etiocholanolone, wherein R and R^1 are each hydrogen and the broken line represents a double bond, or a pharmaceutically or veterinarily acceptable salt thereof.

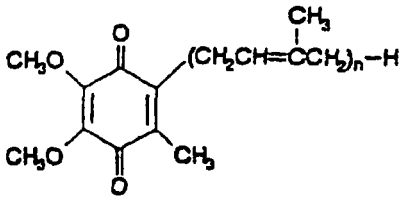
8. The composition of claim 1, wherein the agent comprises a compound of formula I is dehydroepiandrosterone sulphate, wherein R is H, R^1 is SO_2OM and M is a sulphatide group as defined above, and the broken line represents a single bond, or a pharmaceutically or veterinarily acceptable salt thereof.

9. The composition of claim 1, wherein in the compound of formula I, R is halogen selected from the group consisting of Br, Cl and F, R^1 is H, and the broken line represents a double bond, or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

10. The composition of claim 1, wherein the compound of formula I is 16-alpha-fluoro epiandrosterone, or a pharmaceutically or veterinarily acceptable salt thereof.

11. The composition of claim 19, wherein the compound of formula I is dehydroepiandrosterone sulfate or a pharmaceutically or veterinarily acceptable salt thereof.

12. The composition of claim 1, wherein the agent comprises ubiquinone of the chemical formula



(CoQ_n) (II);

wherein n=1 to 12.

13. The composition of claims 1-12, wherein the active agent comprises folinic acid or a pharmaceutically or veterinarily acceptable salt thereof.

14. The composition of claims 1-13, wherein the active agent comprises folinic acid or its salt, and is provided for administration in an amount of about 1 to about 1,000 mg/kg body weight.

15. The composition of claims 1-14, comprising up to about 40% w/w active agent.

16. The composition of claims 1-15, in the form of an inhalable, respirable, intrapulmonary, nasal, topical or transdermal formulation.

17. The composition of claims 1-16, in the form of a buccal, sublingual, dermal, intraocular, intradermal or intraarticular formulation.

18. The composition of claims 1-17, which is a buccal or sub-lingual formulation selected from lozenges further comprising a flavoring agent selected from the group consisting of sucrose, acacia and tragacanth, or pastilles further comprising an inert base selected from the group consisting of gelatin, glycerin, sucrose and acacia.

19. The composition of claims 1-18, which is provided in bulk, or in single or multi-dose form, that may be provided in sealed ampoules or vials.

20. The composition of claims 1-19, which is freeze-dried or lyophilized.

21. The composition of claim 1-17 and 19-20, which is a topical formulation selected from ointments, creams, lotions, pastes, gels, sprays, aerosols or oils, and may further comprise a carrier selected from vaseline, lanoline, polyethylene glycols, alcohols or trans-dermal enhancers.

22. The composition of claim 1-17 and 19-21, which is a transdermal formulation.

23. The composition of claims 1-17 and 19-22, which is provided in a patch.

24. The composition of claims 1-17 and 19-22, which is an iontophoretic formulation selected from iontophoretic solutions or suspensions, which may further comprise a buffer.

25. The composition of claims 1-16 and 19-20, which is suitable for treating asthma, bronchoconstriction, lung inflammation or allergy(ies).

26. The composition of claims 1-16, 19-20 and 25, comprising an inhalable or respirable formulation of particles about 0.5 to about 10 μm in size.

27. The composition of claims 1-16, 19-20 and 25-26, comprising an inhalable or

respirable formulation of particles about 0.5 up to about 5 μm in size.

28. The composition of claims 1-16, 19-20 and 25, comprising a nasal or intrapulmonary formulation of particles about 10 to about 500 μm in size.

29. The composition of claims 1-16, 19-20 and 24-28, which is an aerosol comprising liquid particles.

30. The composition of claims 1-16, 19-20 and 24-28, which is an aerosol comprising solid powdered particles.

31. The composition of claims 1-30, wherein the carrier comprises a hydrophobic carrier.

32. The composition of claims 1-31, wherein the active agent comprises a ubiquinone (CoQn, wherein n=1-10).

33. The composition of claims 1-31, comprising a carrier, and an epiandrosterone of the formula (I) or its salt(s).

34. The composition of claims 1-32, comprising a carrier and a ubiquinone or its salt(s).

35. The composition of claims 1-31 and 33, further comprising a ubiquinone (CoQn, wherein n=1-12), or folinic acid or a salt thereof.

36. A composite, comprising the composition of claims 1-35, and a delivery device.

37. The composite of claim 36, wherein the delivery device comprises an inhaler that delivers individual pre-metered doses of the composition.

38. The composite of claims 36-37, wherein the inhaler comprises a nebulizer or insufflator.

39. The composite of claims 36-38, wherein the delivery device comprises a pressurized inhaler, and the composition comprises a suspension or solution in an aqueous or non-aqueous liquid or an oil-in-water or water-in-oil emulsion.

40. The composite of claims 36-39, wherein the composition is provided in a capsule or cartridge.

41. The composite of claim 40, wherein the capsule or cartridge comprises a pierceable or openable capsule or cartridge.

42. Use of the composition of claims 1-36, in the preparation of an inhalable, respirable, intrapulmonary, nasal, topical or transdermal medicament suitable for preventing or treating a disease or condition of the heart, liver, brain or lung(s), or for regulating adenosine or adenosine receptor levels or reducing sensitivity to adenosine in a subject's tissue (s).

43. The use of claim 42, wherein the medicament is provided for administration by an inhalable, topical, or transdermal route selected from buccal, sublingual, dermal, intraocular, intradermal, transdermal, or intraarticular route.

44. The use of claims 42-43, for the preparation of a respirable, inhalable, nasal or intrapulmonary formulation.

45. The use of claims 42-44, wherein the medicament comprises an inhalable or respirable formulation of particles about 0.5 up to about 10 μm in size.

46. The use of claims 42-45, wherein the medicament comprises a nasal or intrapulmonary formulation of particles about 0.5 up to about 5 μm in size.

47. The use of claims 42-44, wherein the medicament comprises particles about 10 to about 500 μm in size.

48. The use of claims 42-47, wherein the medicament comprises an aerosol.

49. The use of claims 42-48, comprising liquid particles.

50. The use of claims 42-49, comprising solid particles.

51. The use of claims 42-50, wherein the carrier comprises a hydrophobic carrier.

52. The use of claims 42-51, comprising up to about 40% active agent(s).

53. The use of claims 42-52, wherein the active agent comprises an epiandrosterone or its salt(s).

54. The use of claims 42-53, wherein the epiandrosterone or its salt is provided for administration in an amount of about 1 to about 3,600 mg/kg body wt.

55. The use of claims 42-54, wherein the active agent comprises a ubiquinone or its salt(s).

56. The use of claims 42-55, wherein the ubiquinone comprises CoQ_n, wherein n=1 to 12, or its salt(s).

57. The use of claims 42-56, wherein the ubiquinone is provided for administration in an amount of about 1 to about 1,200 mg/kg body weight.

58. The use of claims 42-57, wherein the ubiquinone or salt(s) is used in the preparation of a second medicament for separate but concurrent administration.

59. The use of claims 55-64, wherein the medicament further comprises a folinic acid or its pharmaceutically or veterinarily effective salt(s)

60. The use of claims 42-59, wherein the folinic acid or its salt(s) is provided for administration in an amount of about 1 to about 1,000 mg/kg body weight.

61. The use of claims 42-60, wherein the folinic acid or its salt(s) is used in the preparation of a third medicament for separate but concurrent administration.

62. The use of claims 42-61, wherein the folinic acid or its salt(s) is incorporated into a medicament either with the epiandrosterone or its salt(s) or with the ubiquinone or its salt(s).

63. The use of claims 42-62, wherein the airway disease is associated with bronchoconstriction, or lung inflammation or allergy(ies).

64. The use of claims 42-63, wherein the airway disease comprises bronchoconstriction, or lung inflammation or allergy(ies).

65. The use of claims 42-64, wherein the airway disease is associated with asthma.

66. The use of claims 42-65, wherein the airway disease comprises asthma.

67. The use of claims 42-66, wherein the asthma is associated with the use of a steroid.

68 The use of claims 42-66, wherein the asthma is not associated with use of a steroid.

69. The use of claims 42-68, wherein the disease or condition is associated with anxiety.

70. The use of claims 42-69, wherein the disease or condition comprises anxiety.

71. The use of claims 42-70, wherein the disease or condition is associated with premenstrual syndrome.

72. The use of claims 42-66, wherein the disease or condition comprises premenstrual syndrome.

73. The use of claims 42-73, wherein the disease or condition is associated with a wasting disorder or weight loss.

74. The use of claims 42-64, wherein the disease or condition comprises a wasting disorder or weight loss.

75. The use of claims 42-75, in the treatment of a human or non-human mammal.

76. The use of claims 42-76, in a prophylactic or therapeutic treatment.